The University of Nottingham	**Sponsor Standard Operating Procedure**

Title: **TRIAL MASTER FILE / TRIAL SITE FILE: SET-UP AND MAINTENANCE**

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Author:	Ms Angela Shone
name and position	Research Governance Manager
Authorised by :	Mr Paul Cartledge (Sponsor)
name and position	Head of Research Grants and Contracts
Signature:	**Date :**

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1. Version 1.0 11th November 2008	1. Addition to appendix A of storage of EudraCT confirmation email and SOP Compliance Form RF3 TA008 in TMF

Research and Graduate Services, University of Nottingham,
King's Meadow Campus, Lenton Lane, Nottingham, NG7 2NR
Tel: 0115 8467906, Fax: 0115 9515351, Email: sponsor@nottingham.ac.uk

1. PURPOSE and SCOPE

PURPOSE:
To describe the procedure for setting-up, essential contents of and maintenance of the Trial Master File (TMF) and Trial Site File (TSF) for clinical trials.

SCOPE:
Applicable to all clinical trials that are subject to jurisdiction of the Department of Health Research Governance Framework, 2005, and/or the Medicines for Human Use (Clinical Trials) Regulations, SI 2004, 1031. This SOP is applicable to such clinical trials sponsored by the University of Nottingham (UoN) only.

2. NOTES

2.1 The Trial Master File and Trial Site File are hard copy paper files constructed to contain the 'essential documents' of the trial.
Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

2.2 It is the responsibility of the Chief Investigator to set-up and for the maintenance of a Trial Master File. The day-to day maintenance may be delegated to a suitably trained person and authorised so on the Site Responsibility (Delegation) Log, RF2 TA008.

2.3 The TMF should be established as soon as possible after the UoN has agreed to sponsor a study and maintained from this time until the trial is formally closed and archived as per SOP QA005, Archiving.

2.4 A separate TSF must be set-up in each participating site. The local Principal Investigator is responsible for the maintenance of a Trial Site File. The day-to day maintenance may be delegated to a suitably trained person and authorised so on the Site Responsibility (Delegation) Log, RF2 TA008

2.5 The TSF should be established as soon as the site has all approvals and prior to recruitment of participants at that site. The TSF should be maintained from this time until the trial is formally closed and archived as per SOP QA005, Archiving.

2.6 TMF and TSF contain original and confidential documentation and must be secured accordingly i.e. locked storage with restricted access according to local rules.

2.7 All files shall be made available for internal and external audit purposes as requested by authorised individuals.

3. CROSS REFERENCES

3.1 International Conference on Harmonisation Guideline for Good Clinical Practice, section 8.
3.2 Site Responsibility (Delegation) Log RF2 TA008
3.3 Archiving SOP QA005
3.4 (Suggested) TMF and TSF layout Appendix A

4. PROCEDURE

TMF/TSF Set Up

4.1 Obtain and prepare a set of files (A4 lever arch files or similar and A4 dividers) each labelled with:
- 4.1.1 The trial title and any acronyms to be used
- 4.1.2 The Sponsor's protocol number and any other relevant references
- 4.1.3 The site name and address
- 4.1.4 The REC reference, and where applicable, the MHRA reference.

4.2 Insert labelled dividers to section the files to allow storage of the essential documents as per section 8 of the ICH GCP Guidelines. Suggested layout is given in Appendix A. Each file should contain a table of contents.

Note: The TMF/TSF may consist of more than one volume and each should be labelled appropriately with indications of the sections contained therein.

TMF/TSF Maintenance

4.3 Collate trial documentation and file under the relevant section according to the stage of the trial. Where originals are to be sent to the Chief Investigator for the TMF retain a copy in the TSF.

4.3.1 The documentation to be retained is specified in section 8 of the ICH GCP Guidelines. All are covered in Appendix A.

4.4 All documents must be dated and appropriately authorised by signature where required.

4.5 File all documentation in chronological order within their sections, keeping **all** copies of documents even when updating. When amending documents initial and date any changes, crossing out original text – do not cover with liquid paper or obscure, all text must be legible for audit purposes.

4.6 4.6.1 If a document is missing or unobtainable or a section is inappropriate for a particular trial then add a "file note" dated and signed to this effect and offering an explanation or alternative documentation where possible.

4.6.2 Some sub-sections may become bulky so a separate file may be created. Ensure that this is appropriately labelled and referenced in the main file of its whereabouts.

Archiving of the TMF

4.7 The TMF and TSF are considered "controlled documents". At the end of the trial the TMF/TSF must be archived in accordance with SOP (QA005), Archiving.

5. FLOW CHART

Not applicable

Appendix A

TMF and TSF layout

Section A: Pre-trial opening

A.1 Study Protocol and associated documents (final versions)
Protocol, information sheet, consent form and investigator brochure (where applicable) final versions
Case Report Forms and any other data collection documents, final versions.

A.2 Approval and Agreements
National ethical and competent authority (where applicable) approval
EudraCT email (where applicable)
Local Site Specific Assessment (where applicable)
Local NHS Trust R&D or host organisation approval

Sponsor / Chief Investigator agreement - TMF only
Sponsor / participating site non-commercial agreement

A.3 Staff Participation
Site Responsibility (Delegation) Log, TA008
Curriculum Vitae and Training Records
Attendance at Investigator Training, RF1 TA008
SOP Compliance Form RF3 TA008

A.4 Medical Testing and Pharmacy (where applicable)
Accreditation / certification of supporting Laboratories and pharmacies
'Normal ranges' issued by local laboratories
Investigational product handling (where applicable) – local procedures where not in the study protocol
Investigational product control (where applicable) – local procedures where not in the study protocol
Investigational medicinal product records – certificate of analyses, shipping records, labelling to be used

A.5 Randomization and Blinding
Randomization, blinding and un-blinding procedures where not in the study protocol

Section B: Ongoing Trial

B.1 Study Protocol Amendments and Approvals
Log of study documentation amendments, RF1 TA013
Ethics committee, local host and competent authority approvals of amendments

B.2 Staff Participation

Updated RF1TA008 to include new trial staff
Updated CVs and training records
Updated Attendance at Investigator Training, RF1 TA008

B.3 Informed consent

Signed consent forms of all trial participants
Participant Screening and Enrolment Log RF1 TA011

B.4 Medical Testing and Pharmacy

Updated accreditation / certification of supporting Laboratories and pharmacies
Updated 'normal ranges' issued by local laboratories
Documented evidence of any changes and their implementation to Investigational product handling (where applicable) – local procedures where not in the study protocol
Documented evidence of any changes and their implementation to investigational product control (where applicable) – local procedures where not in the study protocol
Updated investigational medicinal product records – certificate of analyses, shipping records, amended labelling to be used 9if any)

B.5 Case Report Forms and Source Documents

Completed CRFs (copy where originals are sent to a central collection repository) and amended CRFs
Source documents related to the trial

B.6 Serious Adverse Events

SAE reporting forms, RF1 TA014.
CIOMs form (IMP trials only)
SAE reporting forms to the ethics committee
Annual safety reports to ethics committee and regulatory authority (where applicable)
Evidence of notification of actions to be taken and their implementation following a SUSAR (where applicable).

B.7 Biological Materials (if relevant to the study)

List and location of retained samples and Tumour Banking

B.8 Audit and Reporting

Annual progress report(s) to host institution, the ethics committee and competent authority (where applicable)
Monitoring reports
Sponsor audit reports and corrective action forms
Data Monitoring Committee reports (as applicable)
Trial Steering Committee reports (as applicable)
Statistical analyses reports

B.9 Miscellaneous

Correspondence letters, relevant emails etc

Section C: Trial Completion

C.1 Closure

Notification of study closure to the ethics committee
Notification of study closure to the competent authority (where applicable)
Notification of study closure to the host organisation
Notification of study closure to the Sponsor
Treatment allocation and decoding documentation
Documentation of IMP return and/or destruction and pharmacy records

C.2 Audit

Final study report
Final close-out audit report (as applicable)